# PATENT SPECIFICATION

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NO DRAWINGS

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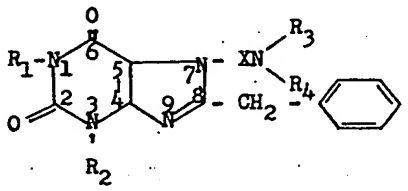
COMPLETE SPECIFICATION

## New Derivatives of Dialkyl Xanthines and the preparation thereof

We, MANUFACTURE DE PRODUITS PHARMACEUTIQUES A. CHRISTIAENS SOCIETE ANONYME, of 60 rue de l'Etuve, Brussels, Belgium, a body corporate organised under the laws of Belgium, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new derivatives of dialkyl xanthines and to the preparation thereof. More particularly, the invention is concerned with new derivatives of 8-benzyl-dialkyl xanthines, and to the preparation thereof.

The new compounds according to the invention are derivatives of 8-benzyl dialkyl xanthines substituted in the 7-position and of the general formula:



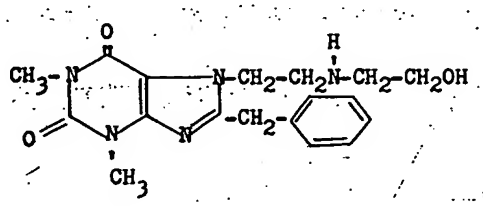
(I)

in which $R_1$ and $R_2$, which may be the same or different, represent alkyl radicals, $R_3$ represents hydrogen or an alkyl, or hydroxyalkyl radical, $R_4$ represents a hydroxyalkyl or aryl hydroxyalkyl radical and X represents an alkylene group.

The invention also provides the acid addition salts of the compounds according to formula I, for example the hydrochlorides.

The following are examples of compounds according to the invention:

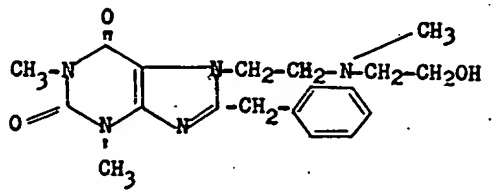
1) 7-(N-β-hydroxyethylamino-ethyl)-8-benzyltheophylline



(II)

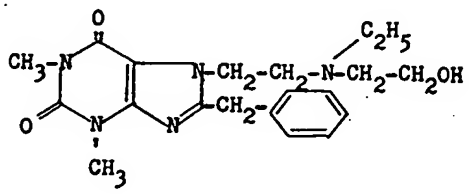
[*Price 4s. 6d.*]

2) 7-(N-methyl-N-β-hydroxyethylamino-ethyl)-8-benzyltheophylline



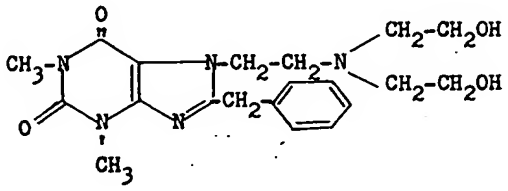
(III)

3) 7-(N-ethyl-N-β-hydroxyethylamino-ethyl)-8-benzyltheophylline



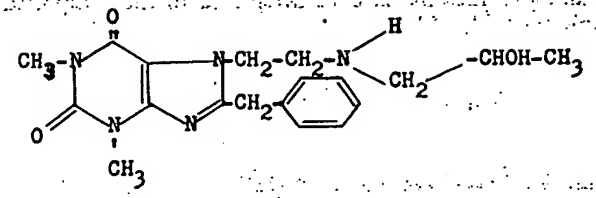
(IV)

4) 7-(N-bis-β-hydroxyethylamino-ethyl)-8-benzyl-theophylline



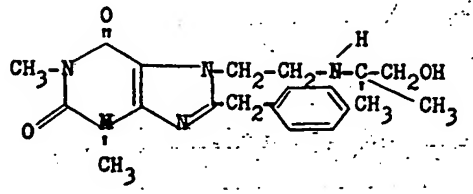
(V)

5) 7-(N-β-hydroxypropylamino-ethyl)-8-benzyl-theophylline



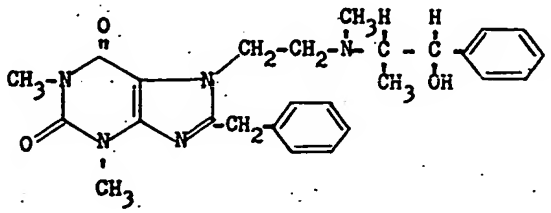
(VI)

6) 7-(N-α-dimethyl-β-hydroxyethylamino-ethyl)-8-benzyl-theophylline



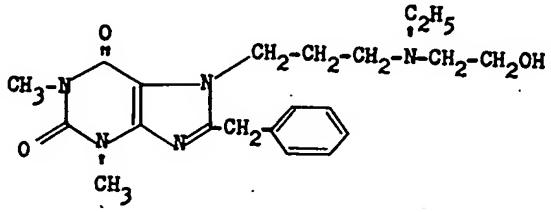
(VII)

7) 7-(N-methyl-N-α-methyl-β-phenyl-β-hydroxyethylamino-ethyl)-8-benzyltheophylline



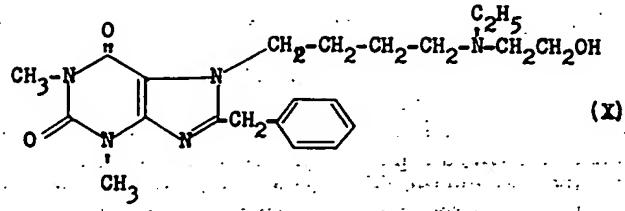
(VIII)

8) 7-(N-ethyl-N-β¹-hydroxyethyl-γ-aminopropyl)-8-benzyltheophylline



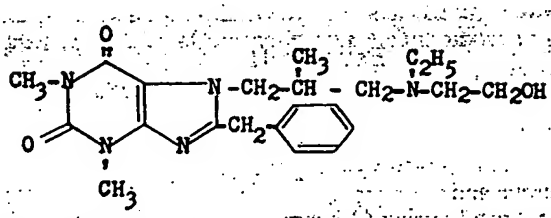
(IX)

9) 7-(N-ethyl-N-β¹-hydroxyethyl-δ-aminobutyl)-8-benzyltheophylline



(X)

10) 7-(N-ethyl-N-β¹-hydroxyethyl-β-methyl-γ-aminopropyl)-8-benzyltheophylline



(XI)

The compounds according to the invention have valuable pharmacological properties and can thus be used as medicines. They can also be employed as intermediate compounds in the synthesis of other pharmacologically active compounds.

Pharmacological tests have shown that the compounds according to the invention have the following activities:

1.— Stimulating action on the central nervous system and particularly on the respiratory and vasomotor system.

2.— Spasmolytic action on the musculature, particularly the musculature of the blood vessels, the bronchia, the biliary system, the intestines and the urethra.

3.— Positive intropic action on the heart.

Under these circumstances, the new compounds may be used for the control of diseases, such as callapse of the circulatory system, angina pectoris, infarctus of

the myocardium, respiratory depression, asthma, various diseases of the lungs, spasms of the biliary system, of the urinary system and of the brain vessels.

The new compounds according to this invention are in general intended for internal administration and may be given perorally or parenterally. Tablets are particularly useful for peroral administration, the active compound being mixed with a solid pharmaceutical carrier. Other possible peroral preparations include capsules and also liquid preparations formulated in a suitable liquid base. Solutions for injection may be made up in sterile pyrogen-free water and the less soluble compounds may be accompanied by dissolving or suspending agents, such as Tween, the word "Tween" being a Registered Trade Mark, or propylene glycol. It is also possible to administer the compounds *per rectum*, incorporated into a suppository base such as coco butter.

The invention also relates to a process for the preparation of compounds of formula I.

According to the invention, a 7-halogenoalkyl-8-benzyl-1,3-dialkyl xanthine can be reacted with a suitable primary or secondary amine of the formula $HNR_3R_4$ wherein $R_3$ and $R_4$ are as defined above. It is preferred to operate in an organic solvent, such as a lower aliphatic alcohol, benzene, xylene, toluene or a ketone, such as acetone or methyl ethyl ketone. It is however also possible to dispense with the use of a solvent and to carry out the reaction in the molten mass of the reagents.

The reaction temperature can vary; it is normally between 80 to 160°C.

The primary and secondary amines are preferably employed in a proportion of at least 2 mols of amine to 1 mol of 7-halogeno-alkyl-8-benzyl-1,3-dialkyl xanthine or in a proportion of 1 mol of amine to 1 mol of 7-halogeno-alkyl-8-benzyl-1,3-dialkyl xanthine, in the presence of an excess of an alkali metal carbonate.

The halohydrates obtained can be converted into free bases in known manner.

The invention is further illustrated by the following Examples:

## EXAMPLE I

Preparation of 7-(N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (Formula II)

A mixture of 3.75 g of 7-(β-bromoethyl)-8-benzyltheophylline, 1.2 cc of ethanolamine and 1.25 cc of absolute ethanol is kept boiling under reflux for 24 hours while stirring. Dilute hydrochloric acid and chloroform are then added and the aqueous layer is separated from the organic phase. This aqueous solution is made alkaline and separated from the chloroform. The chloroformic solution is dried, filtered and evaporated to dryness. An oily residue is obtained which crystallises on addition of petroleum ether, producing white micro-crystals. The hydrochloride of this base, which is prepared under normal conditions, melts at 219 to 220°C (ethanol) and contains 1 molecule of water.

## EXAMPLE II

Preparation of 7-(N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (Formula II)

A mixture of

3.75 g of 7-(β-bromoethyl)-8-benzyltheophylline,

1.8 cc of ethanolamine and

20 cc of xylene is refluxed during 43 hours.

The mixture is treated as described in Example 1. One obtains, with a yield of 90%, the hydrochloride of the compound of formula II melting at 219—220°C, after recrystallization in ethanol.

## EXAMPLE III

Preparation of 7-(N-methyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (formula III)

A mixture of 2.75 g of 7-(β-bromoethyl)-8-benzyltheophylline, 1.5 g of N-methyl-ethanolamine and 10 cc of methylethyl ketone is kept at boiling point for 24 hours while stirring.

By then following the procedure set forth in Example I, 3 g of 7-(N-methyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride are obtained, containing 1 molecule of water and melting at 195.5 to 197°C (ethanol).

EXAMPLE IV

Preparation of 7-(N-ethyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (Formula IV)

A mixture of 127.5 g of 7-(β-chloroethyl)-8-benzyltheophylline, 68.5 g of N-ethyl-ethanolamine and 125 cc of xylene is kept boiling under reflux for 24 hours.

The procedure set forth in Example I is then followed and white micro-crystals are obtained which melt at 80 to 80.5°C.

The yield of 7-(N-ethyl-N-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride, which melts at 185 to 186°C and which is very soluble in water, is 108 g.

EXAMPLE V

Preparation of 7-(N-ethyl-N-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (Formula IV)

A mixture of 3.75 g of 7-(β-bromoethyl)-8-benzyltheophylline, 2 cc of N-ethyl-ethanolamine and 5 cc of xylene is kept at boiling point under reflux for 24 hours.

By then proceeding in accordance with Example I, 2 g of 7-(N-ethyl-N-β-hydroxy-ethylaminoethyl)-8-benzyltheophylline hydrochloride are obtained, which melts at 185 to 186°C.

EXAMPLE VI

Preparation of 7-(N-bis-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (formula V)

A mixture of 3.35 g of 7-(β-chloroethyl)-8-benzyltheophylline, 2.1 g of di-ethanolamine and 10 cc of xylene is kept at boiling point under reflux for 24 hours.

Following the method described in Example I, 3 g of 7-(bis-β-hydroxyethylamino-ethyl)-8-benzyltheophylline hydrochloride are obtained, melting at 156°C.

EXAMPLE VII

Preparation of 7-(N-β-hydroxypropylaminoethyl)-8-benzyltheophylline hydrochloride (Formula VI)

A mixture of 3.35 g of 7-(β-chloroethyl)-8-benzyltheophylline, 2 g of isopropanol-amine and 10 cc of xylene is kept boiling under reflux for 24 hours while stirring.

Using the procedure set forth in Example I, 3 g of 7-(β-hydroxypropylamino-ethyl)-8-benzyltheophylline hydrochloride are obtained, melting at 234 to 234.5°C.

EXAMPLE VIII

Preparation of 7-(N-α-dimethyl-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (Formula VII)

A mixture of 3.35 g of 7-(β-chloroethyl)-8-benzyltheophylline, 2.25 g of 2-methyl-2-amino-1-propanol and 10 cc of xylene is kept boiling under reflux for 24 hours while stirring.

The procedure then followed is in accordance with Example I and 2.15 g of 7-(α-dimethyl-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride are obtained melting at 224 to 225°C.

EXAMPLE IX

Preparation of 7-(N-methyl-N-α-methyl-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride (formula VIII)

5 g of 7-(β-chloroethyl-8-benzyltheophylline, 5 g of ephedrine and 30 cc of xylene is kept boiling under reflux for 5 hours while stirring.

The procedure is then in accordance with Example I, and 7-(N-methyl-N-α-methyl-β-phenyl-β-hydroxyethylaminoethyl)-8-benzyltheophylline hydrochloride is obtained, melting at 226 to 228°C with decomposition.

EXAMPLE X

Preparation of 7-(N-ethyl-N-β¹-hydroxyethyl-γ-aminopropyl)-8-benzyltheophylline hydrochloride (formula IX)

A mixture of 3.4 g of 7-(γ-chloropropyl)-8-benzyltheophylline, 1.1 g of N-ethyl-ethanolamine, 2.5 g of anhydrous potassium carbonate and 25 cc of dry xylene is refluxed during 24 hours. The procedure is then in accordance with Example I. The desired product is obtained with a good yield and melts at 165—168°C after recrystallization in methyl ethyl ketone.

EXAMPLE XI

Preparation of 7-(N-ethyl-N-$\beta^1$-hydroxyethyl-$\delta$-aminobutyl)-8-benzyltheophylline hydrochloride (formula X)

A mixture of 3.6 g of 7-($\delta$-chlorobutyl)-8-benzyltheophylline, 1.1 cc of N-ethylethanolamine, 1.75 g of anhydrous potassium carbonate and 25 cc of dry xylene is refluxed during 24 hours with stirring.

The procedure is then in accordance with Example I. The desired product is obtained with a good yield and melts at 143—145°C after recrystallization in methyl ethyl ketone.

EXAMPLE XII

Preparation of 7-(N-ethyl-N-$\beta^1$-hydroxyethyl-$\beta$-methyl-$\gamma$-amino-propyl)-8-benzyltheophylline hydrochloride (formula XI)

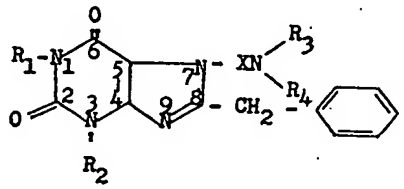
A mixture of 3 g of 7-($\beta$-methyl-$\gamma$-chloropropyl)-8-benzyltheophylline, 1.75 cc of N-ethylethanolamine, 2 g of anhydrous potassium carbonate and 25 cc of xylene is refluxed during 24 hours.

The procedure is then in accordance with Example I. The desired product is obtained with a good yield and melts at 185—187°C after recrystallization in methyl ethyl ketone.

Our co-pending Application, No. 14251/60 (Serial No. 947,494), claims compounds with the same skeleton as those claimed in this application but having a straight chain or branched chain halogenoalkyl radical, having a maximum of 4 carbon atoms, at position 7. Those compounds may be used as starting materials in the preparation of the compounds of the present invention.

WHAT WE CLAIM IS:—

1. As new compounds, derivatives of 8-benzyl dialkyl xanthines substituted in the 7-position and of the general formula:



(I)

in which $R_1$ and $R_2$, which may be the same or different, represent alkyl radicals, $R_3$ represents hydrogen or an alkyl, or hydroxyalkyl radical, $R_4$ represents a hydroxyalkyl or aryl hydroxyalkyl radical and X represents an alkylene group, and the acid addition salts thereof.

2. 7-(N-$\beta$-hydroxyethylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

3. 7-(N-methyl-N-$\beta$-hydroxyethylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

4. 7-(N-ethyl-N-$\beta$-hydroxylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

5. 7-(N-bis-$\beta$-hydroxyethylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

6. 7-(N-$\beta$-hydroxypropylamino-ethyl)8-benzyltheophylline and the acid addition salts thereof.

7. 7-(N-$\alpha$-dimethyl-$\beta$-hydroxyethylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

8. 7-(N-methyl-N-$\alpha$-methyl-$\beta$-phenyl-$\beta$-hydroxyethylamino-ethyl)-8-benzyltheophylline and the acid addition salts thereof.

9. 7-(N-ethyl-N-$\beta^1$-hydroxyethyl-$\gamma$-aminopropyl)-8-benzyltheophylline and the acid addition salts thereof.

10. 7-(N-ethyl-N-$\beta^1$-hydroxyethyl-$\delta$-aminobutyl)-8-benzyltheophylline and the acid addition salts thereof.

11. 7-(N-ethyl-N-$\beta^1$-hydroxyethyl-$\beta$-methyl-$\gamma$-aminopropyl)-8-benzyltheophylline and the acid addition salts thereof.

12. A process for the preparation of a derivative of 8-benzyl dialkyl xanthine according to claim 1, in which a 7-halogenoalkyl-8-benzyl-1,3-dialkyl xanthine is

reacted with an amine of the formula $HNR_3R_4$ in which $R_3$ and $R_4$ have the meanings defined above.

13. A process according to claim 12, in which a proportion of at least 2 mols of amine to 1 mol of 7-halogeno-alkyl-8-benzyl-1,3-dialkyl xanthine is used.

14. A process according to claim 12, in which a proportion of 1 mol of amine to 1 mol of 7-halogeno-alkyl-8-benzyl-1,3-dialkyl xanthine is used, in the presence of an excess of an alkali metal carbonate.

15. A process for the production of compounds as claimed in claim 1 substantially as described with reference to any of the Examples.

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